administering [two antineoplastic agents] epirubicin and docetaxel, and a pharmaceutically acceptable carrier, a pharmaceutically acceptable diluent, or combinations thereof, and exemestane and a pharmaceutically acceptable carrier, pharmaceutically acceptable diluent or combinations thereof, wherein epirubicin, docetaxel, and exemestane are present in superadditive antitumor effective amounts.

74. (Original) The method according to claim 72, wherein the antineoplastic agent is epirubicin.

75. (Original) The method according to claim 72, wherein the antineoplastic agent is docetaxel.

76. (Original) The method according to claim 72, wherein an effective antineoplastic amount of epirubicin ranges from about 20 mg/m2 to about 200 mg/m and an effective antineoplastic amount of docetaxel ranges from about 50 mg/m2 to about 100 mg/m2.

77. (Original) The method according to claim 76, wherein the neoplastic agent and the aromatase inhibitor exemestane is administered orally, and is administered from about 5 to about 200 mg.

78. (Original) The method according to claim 72, wherein the amount of aromatase inhibitor exemestane ranges from about 10 to about 25 mg.

79. (Original) The method according to claim 76, wherein the antineoplastic agent and the steroidal aromatase inhibitor exemestane are administered parenterally, and the aromatase inhibitor is administered from about 5 to about 500 mg.

80. (Original) The method according to claim 72, wherein when administered subcutaneously, the amount of aromatase inhibitor exemestane is about 20 mg/Kg/day.

81. (Original) The method according to claim 80, wherein when administered intravenously, the amount of antineoplastic epirubicin is 1 or 3 mg/Kg/week.

82. (Original) The pharmaceutical composition according to claim 80, wherein when administered intravenously, the amount of antineoplastic docetaxel is about 1.5 mg/Kg/week.

REMARKS

Favorable reconsideration and allowance are respectfully requested. Claims 50-82 are pending. By this amendment, claim 51, 62, and 73 have been amended to address the Section 112 rejection discussed below. Therefore, the amendments to the claims do not introduce new matter. Claims 50-82 remain pending and at issue.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 51, 62, and 73 were rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite. Original claims 51, 62, and 73 refer to "two antineoplastic agents" and the Examiner asserted that "there is insufficient antecedent basis for this limitation in the claim since it is unclear as to which are 'two antineoplastic agents' and whether these 'two antineoplastic agents' are epirubicin and docetaxel recited in the independent claims or something else." (Office Action at 3).

Applicants have amended claims 51, 62, and 73 to address this rejection by explicitly referring to the administration of both epirubicin and docetaxel in combination with exemestane. Thus, the rejections under Section 112 are moot in view of Applicants' amendments to the claims.

Rejection Under 35 U.S.C. § 103

Claims 50-82 were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Buzzetti et al., U.S. Patent No. 4808616 ("Buzzetti") in view of Tognella et al., U.S. Patent No. 4871528 ("Tognella") and Shashoua et al., U.S. Patent No. 5,795,909 ("Shashoua"). The Examiner contends that Buzzetti discloses exemestane as an agent that is useful in the treatment of hormone-dependent cancers in mammals. Buzzetti is also cited as showing that the effective amount of exemestane is about 10 to about 150-200 mg/day. The Examiner concedes that while "Buzzetti . . . does not expressly disclose the employment of exemestane in combination with the instant antineoplastic agent, epirubicin or docetaxel in pharmaceutical compositions and methods for treating breast cancer in humans and lowering the side effects in humans." (Office Action at 4.) Tognella is cited as a disclosure of mono- or polychemotherapy against tumors. The Examiner states that Tognella discloses that known anti-tumor agents, such as epirubicin, used in combination with other agents, is useful in the treatment of breast cancer to reduce the side effects caused by anti-tumor therapy. The Examiner also relies on Tognella as a disclosure of the synergistic effects observed using multiple agents in combination therapy. Finally, the Examiner relies on Shashoua as a disclosure of numerous antineoplastic agents, including but not limited to docetaxel and epirubicin, in combination with aromatase inhibitors, including but not limited to exemestane, are useful in the treatment of breast cancer to reduce side effects.

Therefore, the Examiner concludes that

> It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ exemestane in combination with the instant antineoplastic agent, epirubicin or docetaxel in pharmaceutical compositions and methods for treating breast cancer in humans and lowering the side effects in humans.
>
> One having ordinary skill in the art at the time the invention was made would have been motivated to employ exemestane in combination with . . . epirubicin or docetaxel in pharmaceutical compositions and methods for treating breast cancer in humans and lowering the side effects in humans, since the instant antineoplastic agents such as epirubicin and docetaxel, and exemestane, alone and/or combination, are known to be useful in pharmaceutical compositions and methods for treating breast cancer in humans and/or lowering the side effects in humans based on the prior art.

Office Action at 5.

Applicants respectfully traverse this rejection. The Examiner's argument concerning the allegedly unpatentability of the claimed compositions and methods is predicated on an "obvious to try" standard, which is impermissible. The instant claims are actually fairly narrowly crafted; they specifically require the use of exemestane in combination with docetaxel, epirubicin or both, wherein each agent is administered in superadditive amounts. This is simply not taught or

suggested in the prior art, nor would one skilled in the art find the motivation or reasonable expectation of success in the prior art to make this specific combination. All that the prior art shows is that each of the agents were known as of the filing date and that it was also known to combine certain antineoplastic agents for a therapeutic benefit, but that does not amount to the motivation or reasonable expectation of success to make the specific claimed combinations to achieve a superadditive benefit. The cited art simply does not provide the motivation or reasonable expectation of success to make the claimed invention.

Buzzetti simply discloses exemestane and it states that it may be used in combination with other agents, without more disclosure than this simple declarative statement. Tognella does not remedy this deficiency because it discloses the generic benefits of combination chemotherapy, but one skilled in the art would not interpret Tognella as saying that anytime an oncologist administers more than two antineoplastic agents he/she will necessarily achieve a superadditive effect. This is too simplistic an interpretation of the Tognella. Finally, Shashoua does not remedy the deficiencies of either Buzzetti or Tognella. All that Shashoua provides is a list of possible antineoplastic agents and the general instruction that the agents may be used alone or in combination. Shashoua does not specifically direct the skilled artisan to select docetaxel and/or epirubicin from among the many agents listed, and use these agents with exemestane, also one aromatase inhibitor of a list of a variety of aromatase inhibitors, nor does Shashoua provide the skilled artisan a reasonable expectation of successfully achieving a superadditive effect, such as that disclosed in Tables 1 and 2 of the instant application. All that these references provide the skilled artisan is an argument that it would have been obvious to try the claimed combinations.

In view of the foregoing remarks, Applicants submit that the rejections under Sections 103 should be withdrawn.

Double Patenting Rejection(s)

Claims 50-82 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 6-53 of copending application USSN 10/363935. As this is a provisional rejections, Applicants request that the Examiner hold the rejection in abeyance pending the determination of allowable subject matter in each application. If the instant application should be placed in condition for allowance prior to the determination of allowable subject matter in the copending application, the MPEP provides that the instant application should be allowed to issue and the double patenting rejection may be maintained in the remaining pending application.

CONCLUSION

Favorable consideration of the foregoing amendments and remarks are respectfully requested. If, after consideration of this Amendment the Examiner maintains that there are issues

that remain an impediment to allowance, he is invited to telephone the undersigned to discuss such issues.

Respectfully submitted,

Date: 9-26-05

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